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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,082	07/10/2000	CHENICHERI H. NAIR	S-00	5840
23713	7590	01/11/2005	EXAMINER	
GREENLEE WINNER AND SULLIVAN P C			MITCHELL, GREGORY W	
4875 PEARL EAST CIRCLE			ART UNIT	PAPER NUMBER
SUITE 200				1617
BOULDER, CO 80301				

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicant No.	Applicant(s)	
	09/463,082	NAIR ET AL.	
	Examiner	Art Unit	
	Gregory W Mitchell	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 20 September 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 31,33-35,61,64,68,71 and 80-85 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 31,33-35,61,64,68,71 and 80-85 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>09/20/04</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

This Office Action is in response to the remarks, amendments and RCE filed on September 20, 2004. Claims 31 and 80-82 have been amended. Claims 84 and 85 have been added. Claims 31, 33-35, 61, 64, 68, 71, and 80-85 are pending and are examined herein.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 20, 2004 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 33-35, 61, 64, 68, 71, and 80-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a NEW MATTER rejection. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrase “wherein said particles bind *directly* to said fibrin” (emphasis added) does not have antecedent basis in the specification, claims, and/or drawings as originally filed. Applicant points Examiner to page 10, lines 10-12; Examples 3-7; and page 14, line 20 to page 16, line 9, but Examiner finds no support for the current claim language therein. For examination purposes, Examiner will consider the claims as containing the limitation: “wherein said particles bind directly to said fibrin”.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 31, 33, 34, 71, and 80-85 rejected under 35 U.S.C. 103(a) as being unpatentable over Watson et al. (WO 93/15768) in view of Reno et al. (USPN 5217705).

The instant invention is directed toward a method for the *in vivo* detection of fibrin, comprising administration to a patient an effective amount of a detectable reagent comprising discrete particles dispersed in a pharmaceutically or veterinarily acceptable carrier, diluent, excipient, adjuvant or combination thereof, wherein said particles comprise a detectable marker encased in at least two layers of carbon, wherein the outer surface of said particles allows for a stable chemical association with an aqueous medium and wherein upon administration of said reagent said particles are dispersed in

the aqueous medium and form a stable colloid; binding said particles directly to said fibrin; and detecting the presence of said detectable marker in said patient.

Watson et al. teaches that non-diamond carbon allotropes, such as fullerenes, graphite and amorphous carbons, are used as diagnostic agents (page 1). Molecular mesh compounds (e.g. graphite) is taught for use as a contrast enhancing agent in imaging modalities (page 3). These mesh compounds are taught to be optionally attached to biomolecules (e.g. proteins, antibodies, cell adhesion molecules, etc.) and are taught to be carriers for signal forming entities, e.g. chromophores, fluorophores, radiolabels, magnetic labels, etc. (pages 3, 4 and 6). In graphite, it is taught that the diagnostic entity is intercalated between adjacent webs (page 6). Therefore, it is noted, the graphitic label containing entity obviously possesses at least two layers. The diagnostic agents of the Watson et al. are taught to be useful in vivo (in humans or non-human animals) and are taught to be administered by any convenient route, e.g. iv, im, ip, or oral (pages 26-27). It is noted that Watson et al. specifically teaches the targeting of the blood pool with the diagnostic agent (page 27). The diagnostic agents are taught to be formulated with conventional pharmaceutical or veterinary formulation aids (e.g. surfactants) and that dispersions (colloids) may be in an acceptable carrier media, e.g. water or saline (page 27). It is pointed out that Watson et al. specifically states that “[t]he non-diamond carbon allotropes useful according to the invention include the long known graphite and amorphous carbons ...” (page 5). Watson et al. does not specifically teach the targeting of fibrin with the diagnostic agent taught therein.

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Reno et al. teaches a method of diagnosing blood clots using fibrin-binding proteins. The proteins are attached to detectable substances, such as radioisotopes of iodine, bromine, fluorine or 99mTc. See col. 5, lines 20-56.

It would have been obvious to one of ordinary skill at the time of the invention to utilize a radiolabeled graphitic mesh entity of Watson et al. attached to a protein of Reno et al. in a method for detecting fibrin in a patient because (1) Watson et al. teaches the administration of the carbon allotropes of the invention therein to humans and non-human animals for diagnostic purposes; (2) Watson et al. teaches that the diagnostic agents taught therein may be attached to biomolecules such as proteins and cell adhesion molecules; (3) Watson et al. teaches that the carbon allotrope diagnostic entity of the invention therein is used as a carrier for radiolabels; (4) Reno et al. teaches administration of a diagnostic agent for the detection of fibrin; and (5) Reno et al. teaches the attachment of a fibrin-binding protein attached to a detectable substance such as a radiolabel. One would have been motivated to administer the diagnostic entity of Watson et al. attached to a protein of Reno et al. for the detection of fibrin because of an expectation of success in enhancing imaging modalities, as taught by Watson et al., in detecting fibrin, as taught by Reno et al.

It is noted that the claim language of claims 31, 80, and 81 stating that the outer surface of said particles "comprises graphitic carbon" does not limit the outer surface of the particle from comprising something other than graphitic carbon, such as a fibrin-binding protein.

It is further noted that the limitations of claims 82 and 83 are drawn to a method of preparing the diagnostic agent to be used in the method claimed therein. Where the same method utilizing the same agent is rendered obvious by the prior art, no patentable weight is given to the method of preparing the agent to be used in the method claimed. Accordingly, since the claims are drawn to a method of detecting fibrin with a product described therein, no patentable weight is given to the means of preparing that product.

It is also pointed out that the limitation of 2-20 layers is rendered obvious by the fact that the graphitic entity of Watson et al. obviously teaches at least two layers, as discussed above. Accordingly a graphitic entity comprising 2-20 layers would have been obvious at the time of the invention because where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

It is noted that where the claimed and prior art products are identical or substantially identical in structure or composition a *prima facie* case of obviousness has been established. MPEP 2112. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Accordingly, it is Examiner's position that the particles rendered obvious by Watson et al. and Reno et al. selectively bind fibrin. It is also noted that Reno et al. indicates that the proteins to be used therein are "fibrin-binding proteins," indicating that said proteins selectively bind fibrin.

Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Watson et al. and Reno et al. as applied to claims 31, 33, 34, 71, and 80-85 and further in view of Doherty et al. (USPN 3952321).

Watson et al. and Reno et al. apply as disclosed above. In addition to aqueous solutions, Watson et al. also teaches administration of parenteral solutions such as sodium chloride solutions and Ringer's solution (page 30). Neither reference specifically teaches an aqueous solution comprising glucose in water.

Doherty et al. teaches water, Ringer's solution, glucose in water, and isotonic sodium chloride as acceptable vehicles for in vivo administration of active agents (col. 18, line 57-col.19, line 9).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the glucose in water, taught by Doherty et al., for the vehicles taught by the combined references because the combined references teach water, sodium chloride and Ringer's solution as useful in the invention taught therein. Furthermore, Doherty et al. teaches that water-in-glucose is an interchangeable vehicle with water, sodium chloride, and Ringer's solution in in vivo administration. One would have been motivated to substitute one of the aqueous solutions of Watson et al. with the glucose in water solution of Doherty et al. because of an expectation of similar success in in vivo administration.

Doherty et al. does not specifically teach glucose in an amount of 5% but where general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

Claims 61 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watson et al. and Reno et al. as applied to claims 31, 33, 34, 71, and 80-85 above and further in view of both Park et al. (USPN 5330768) and Penfold et al. (J. Phys. Chem.).

Watson et al. and Reno et al. apply as disclosed above. Neither teaches a coating of C16EO6.

Park et al. teaches films for drug delivery comprised of poly(lactic acid) and polyethyleneoxide and polypropylene oxide. It is taught that the water content of the polymer can be controlled by blending different kinds of block polymers and by adjusting ratios. These compounds also exhibit a wide range of hydrophilicity/hydrophobicity. See col. 3, lines 4-50.

Penfold et al. teach C16EO6 as a known, beneficial nonionic polyethylene oxide surfactant. See abstract and page 18133.

It would have been obvious to one of ordinary skill in the art at the time of the invention to coat a diagnostic particle rendered obvious by Watson et al. and Reno et al. with a C16E06 because (1) Watson et al. teaches that surfactants may be used with the diagnostic agents of the invention taught therein; (2) Penfold et al. teaches that C16EO6 is a known polyethylene oxide surfactant; and (3) Park et al. teaches that films of polyethylene oxides are known to be used for forming films on agents administered in vivo. One would have been motivated to administer a particle rendered obvious by Watson et al. and Reno et al. coated with C16EO6 because of an expectation of

success in achieving extended release of the agent, as taught by Park et al. (Abstract), and achieving a desired hydrophilicity/hydrophobicity, as taught by Park et al.

Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Watson et al. and Reno et al. as applied to claims 31, 33, 34, 71, and 80-85 above, and further in view of The Handbook of Cosmetic Science and Technology.

Watson et al. and Reno et al. apply as disclosed above and fail to specifically teach nanocolloids.

The Handbook of Cosmetic Science and Technology teaches the surface chemistry of colloid systems. It is taught that a reduction in size of the dispersed phase particles increases the stability of the colloid. See pages 67-69.

It would have been obvious to one of ordinary skill in the art at the time of the invention to teach the dispersion of the combined references as nanodispersions, wherein a dispersion is in the form of a colloid, because of the expectation of achieving a more stable formulation.

Response to Arguments/Amendments

Applicant's arguments filed September 20, 2004 have been fully considered but they are not persuasive.

Applicant argues that Watson et al. and Reno et al. "do not disclose or even suggest the specific binding of the carbonaceous particles of the present invention to fibrin which serves the basis of the step of 'binding said diagnostic particles to said

fibrin' in the rejected claims." Applicant further argues that "nowhere in [the references] is the capability of carbonaceous particles, such as graphitic carbon particles, to bind to fibrin mentioned or suggested, let alone is the selectivity and high affinity of this interaction described." These arguments are not persuasive because Applicant is arguing limitations that are not present within the claims. It is pointed out that the claims are drawn to a particle *comprising* an outer surface of graphitic carbon. Accordingly, the outer surface of the particle may also comprise something else, such as a fibrin-binding protein. Furthermore, it is pointed out that Applicant's own specification indicates that in a preferred embodiment, the surface of the graphitic entity is chemically modified (see pages 3-4 of Applicant's specification).

Applicant argues that because Watson et al. and Reno et al. do not teach the process of preparing the graphitic agent to be used in the instant invention that the claims are not rendered obvious by Watson et al. and Reno et al. As discussed above, where administration of the same composition to the same population for the same purpose is rendered obvious by the prior art, no patentable weight is given to the process of making said composition.

Applicant argues that the recitation of the limitation of "about 2 to 20 layers of carbon" distinguishes the methods of the amended claims from the methods of the prior art. These arguments are not persuasive for the reasons set forth in the instant rejection, namely that Watson et al. obviously teaches at least 2 layers of carbon.

Regarding the selective binding of the graphitic diagnostic agents, Applicant argues, "the Examiner may not properly rely on the inherency of this unknown and

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nonobvious characteristic to support the present nonobviousness rejection under 35 U.S.C. 103(a)." This argument is not persuasive because, as pointed out in the instant Office Action, Reno et al. specifically teaches fibrin-binding proteins. It is also noted that Watson et al. and Reno et al. combine to teach the same diagnostic agent administered to the same population for the same purpose (detecting fibrin) as that claimed in the instant invention. Accordingly, any property exhibited by said diagnostic agent would obviously be present as well.

Applicant argues that the cumulative teachings of Watson et al. and Reno et al. do not enable the synthesis of graphite surfaces having biologically active, surface bound fibrin binding proteins. This argument is not persuasive because Examiner cannot comment on the enablement of the teachings of Watson et al. It is pointed out that Watson et al. teaches that the non-diamond carbon allotropes may be optionally attached to biomolecules, including proteins, as discussed above. Accordingly, it is Examiner's position that it is within the skill of the art to attach biomolecules to the non-diamond carbon allotropes of Watson et al., including graphitic entities.

Finally, Applicant argues, "a person of ordinary skill in the art would [not] be motivated to attempt to derivatize the extremely graphitic surfaces of Watson et al. to incorporate the fibrin-binding proteins of Reno et al." and "the skilled artisan would [not] have a reasonable expectation of successfully achieving the composition relied upon by the Examiner in the present rejections because a person of ordinary skill in the art would not expect that fibrin binding proteins can be chemically coupled to inert carbon surfaces, such as graphitic carbon surfaces, without affecting the protein's structure and

its ability to selectively bind to fibrin." These arguments are not persuasive for the reasons set forth in the instant rejection. It is specifically noted that Watson et al. teaches that proteins and cell adhesion molecules may be bound to the non-diamond carbon allotropes of the invention taught therein. It is also noted that Reno et al. teaches that the proteins of the invention taught therein may be bound to detectable substances. Accordingly, it is Examiner's position that there would be motivation to bind the diagnostic agent of Watson et al. to a biochemical molecule such as a protein or a cell adhesion molecule because of an expectation of success in achieving a functional diagnostic agent as Watson et al. teaches the binding of the graphitic entity to a protein or cell adhesion molecule and Reno et al. teaches the binding of a fibrin-binding protein to a detectable substance.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8:30 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm



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